REMARKS

This responds to the Office Action dated October 23, 2008.

Claims 1-2 and 5-6 are amended, no claims are canceled, and claims 9-16 are added; as a result, claims 1-16 are now pending in this application.

Claim 1 was amended to direct the subject matter of the claim to the elected Group 4. Claim 2 was amended to direct the subject matter of the claim to the elected Group 4, and to clarify the proviso at the end of the claim. New claims 9-16 were added to further claim aspects of the invention. Support for new claims 9-16 can be found in original claim 1, in Figure 4, and throughout the specification. Accordingly, no new matter has been added.

For the Examiner's convenience, Applicant notes that new claims 9-12 are directed to inhibitors of fatty acid amide hydrolase where the binding subunit C is C1-C10 alkyl. New claims 13-15 are directed to inhibitors of fatty acid amide hydrolase where the binding subunit C is an alkene. New claims 16-18 claims dependent upon original claim 4.

Election / Restrictions

At page 2, the Office Action states that Applicant elected Group 1 in the reply filed August 29, 2008. However, Applicant elected Group 4, claims 1-4, drawn to compounds of formula A-B-C where het is an oxazole moiety and the linkage subunit B does not include heteroatoms. See page 16, line 1 of the reply filed August 29, 2008.

As discussed below, Applicant respectfully submits that the claims are in condition for allowance. Applicant requests rejoinder of claims 5-9 upon allowance of claims 1-4.

§ 112 Rejection of the Claims

Claims 1 and 2-3 were rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite. This rejection is respectfully traversed.

At page 3, lines 1-3, the Office Action stated that the terms 'proviso' in the context of the term 'optionally' was confusing. While Applicant disagrees with the assertion, Applicant has deleted the phrase "with the following proviso" and added the term "wherein" to clarify that section of the claim. The last line of the claim that included the term "proviso" and "optionally"

was also deleted. Accordingly, claim 1 is clear and definite. Reconsideration and withdrawal of the rejection is respectfully requested.

§ *102 Rejection of the Claims*

Claims 1-3 were rejected under 35 U.S.C. § 102(b) as being anticipated by Dondoni et al., *Journal of Organic Chemistry* (1987), 52(15), 3413-20 ("Dondoni"). This rejection is respectfully traversed.

Claim 1 was amended to remove the last line, which stated "with a proviso that C is optionally C1-C10 alkyl". Claim 1 therefore does not encompass the compound suggested by the Examiner, which corresponds to Entry 10 in Table II at page 3416 of Dondoni.

Claim 1 was also amended to remove the term "alkenyl" from the definition of binding subunit C (see the last paragraph of claim 1). Claim 1 therefore does not encompass the compound suggested by the Examiner, which corresponds to Entry 11 in Table II at page 3416 of Dondoni.

New claims 9-16 have been added. Independent claims 9 and 13 do not encompass any compound disclosed by Dondoni, and specifically the two compounds noted by the Examiner, at least in part, because R^2 cannot be phenyl. Therefore, the disclosure of Dondoni does not anticipate Applicant's claims.

Reconsideration and withdrawal of the rejection is respectfully requested.

§ *103 Rejection of the Claims*

The Boger PNAS Document.

Claims 1-4 were rejected under 35 U.S.C. § 103(a) as being obvious over Boger et al., *Proceedings of the National Academy of Sciences* 97(10), 2000, 5044-5049 ("the Boger PNAS document"). This rejection is respectfully traversed.

At page 5 of the Office Action, the Examiner identified compounds **21**, **23**, and **11** as the closest prior art. However, these compounds differ significantly from the claimed compounds because the either do not include a C4 or C5 substituent, or they include a C4,C5 benzo ring substitution. These differences are substantial because they occur in the region of inhibition subunit A. Additionally, Applicant notes that claim 1 has been amended such that the binding

subunit C does not encompass the alkene moiety disclosed by the Boger PNAS document's Table 1 at page 5045, further differentiating claims 1-4 from the cited document.

The Office Action asserts that "one skilled in the art... would be motivated to make additional analogs of compound **11** substituted at the 4,5-positions, because Boger's teaching suggests that substitution at the 4 and 5 positions away from the activated carbonyl functionality as found in compounds **21** and **23** retains biological activity and thus provides medicinal chemistry opportunities to optimize physical properties of known compound **11**." Applicant strongly disagrees with this assertion.

The Boger PNAS document teaches that the benzoxazole region of the active site is very sensitive to small changes. For example, adding a methyl group to any location on compound **23** greatly diminishes or completely destroys all activity (see the Boger PNAS document at page 5046, Table 2). Therefore, the Boger PNAS document does not teach that "substitution at the 4 and 5 positions away from the activated carbonyl functionality as found in compounds **21** and **23** retains biological activity". The Boger PNAS document teaches that such substitution actually destroys activity in the cases of compounds 21, 22, and 24, and renders compound **23** 20 fold less active. Because compound **10** is more active than compound **23**, which is more active than substituted versions of compound **23** (i.e., compounds **25-28**), one would **not** be motivated to make further substitutions at the 4,5 position of the oxazole moiety of compound **10**. To suggest otherwise would employ impermissible hindsight. Additionally, of all possible substituents that could be employed at the C4 and C5 positions of an oxazole moiety, the Office Action fails to explain why one would select the substituents claimed by Applicant, for example, the activity of the compounds illustrated in Figure 4.

Thus, compounds **21**, **22**, and **24** of the Boger PNAS document are inactive FAAH inhibitors. Although the Boger PNAS document compound **23** is active, the document does not teach that C4 or C5 substitution would result in enhanced activity, and in fact, teaches quite the opposite. Compound **23** is 20 fold less active than compound **10**. It would therefore appear to one skilled in the art that the region of inhibition subunit A has already been optimized and other portions of the molecule would be more likely to provide opportunities for optimization. Maintaining otherwise suggests an impermissible use of hindsight, when it is Applicant that has discovered the important claimed compounds. With respect to inhibition subunit A, claims 1-4

move in the opposite direction from the teachings of the Boger PNAS document because binding subunit C does not include the alkene moiety of the corresponding binding subunit C. The Boger PNAS document does not teach or suggest a way to modify the disclosed compounds in a manner necessary to arrive at Applicant's claimed invention, and one skilled in the art would not know what combination of substitutions, deletions, or additions to make to arrive at the claimed compounds.

Additionally, none of the inhibitors described by the Boger PNAS document have been show to be active *in vivo*. The specification shows that Applicant's compounds are improvements over the prior art, and do have *in vivo* activity, as described at page 12, line 17 to page 13, line 13, and as illustrated in Figures 11-14. This *in vivo* activity further demonstrates the non-obvious nature of the claimed invention.

Furthermore, Applicant has determined that the claimed compounds exhibit new and unrecognized selectivity for FAAH versus TGH and KIAA 1343, which are off site target enzymes. Inhibition of these enzymes is significantly deleterious to therapeutic activity, thus therapeutic agents that do not inhibit TGH and KIAA 1343 provide significant advantages. The claimed compounds do not inhibit TGH and KIAA 1343 because of their C4 or C5 substitution, while compounds **10** and **11** of the Boger PNAS document exhibit potent TGH inhibition. Accordingly, even if a *prima facie* case of obviousness is maintained, it can be overcome by these unexpected results.

Therefore, Applicant's claimed compounds are structurally non-obvious in view of the Boger PNAS document and provide significantly superior activity and selectivity compared to the compounds described by the Boger PNAS document. Reconsideration and withdrawal of the rejection is respectfully requested.

Applicant notes that claim 4 was rejected as allegedly being obvious over the Boger PNAS document, however the Office Action does not indicate why claim 4 would be obvious over the Boger PNAS document. The Boger PNAS document does not provide any teaching or suggestion that would motivate one skilled in the art to modify the binding subunit C to include the claimed phenyl group **and** to omit the site of unsaturation, **in addition to** substituting the oxazole moiety only at the C5 position with 2-pyridyl (and not any other group). Furthermore, the data shown in the Boger PNAS document indicate that removing the site of unsaturation in

the portion of the molecule corresponding to binding subunit C actually decreases FAAH inhibitory activity (see, e.g., Table 4 at page 5046). Accordingly, claim 4 and its dependent claims 16-18 are further non-obvious in view of the Boger PNAS document. Reconsideration and withdrawal of the rejection of claim 4 is respectfully requested.

Applicant further notes that new claims 9-12, directed to inhibitors of fatty acid amide hydrolase where the binding subunit C is C1-C10 alkyl, are non-obvious for the same reasons, namely that binding subunit C does not include an unsaturated moiety, and the data shown in the Boger PNAS document indicates that removing the site of unsaturation in the portion of the molecule corresponding to binding subunit C actually decreases FAAH inhibitory activity, and there is not teaching or suggestion in the Boger PNAS document that FAAH inhibitors should include a 2-pyridyl group at the oxazole C5 position. Accordingly, claims 9-12 are believed to be in condition for allowance, and notification to that effect is earnestly requested.

Finally, new claims 13-15 are directed to inhibitors of fatty acid amide hydrolase where the binding subunit C is an alkene, such as FAAH inhibitor 70, illustrated in Applicant's Figure 9, which is 15 fold more active than the corresponding C5 unsubstituted oxazole compound. Claims 13-15 are therefore also believed to be in condition for allowance, and notification to that effect is earnestly requested.

Link in View of The Boger PNAS Document.

Claims 1-3 were rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Link et al. (U.S. Patent No. 6,576,630) ("Link") in view of Boger et al. ("the Boger PNAS document"). This rejection is respectfully traversed.

At page 6 of the Office Action, the Examiner identified compound **11**, found at column 55, lines 57-58 of Link, as the closest prior art. The Office Action asserts that "one skilled in the art of drug design of protease inhibitors engaged in making inhibitors of FAAH, would be motivated to make additional analogs of compounds of Link et al. with the modification (deletion) of groups as taught by Boger et al.... because the critical major portion of the heterocycle-ketone arrangement is present in the teachings of both the references and the interaction of the substrate (inhibitor) with the catalytic triad is not adversely dependent on the

substitution on the carbon alpha to the keto group providing medicinal chemistry opportunity for optimizing receptor (enzyme) selectivity." Applicant strongly disagrees with this assertion.

Link teaches protease inhibitor compounds, including several genera and hundreds of specific examples thereof. Link teaches compound **11** as an inhibitor of cysteine protease. Applicant notes that FAAH is not a cysteine protease. It is not apparent why one would select a protease inhibitor to optimize a FAAH inhibitor. FAAH does not recognize peptide substrates and its catalytic active residues are Lys-Ser-Ser, which is significantly different than proteases and even conventional Serine hydrolases. Therefore it is unclear why one would select any compound taught by Link to combine with the teachings of the Boger PNAS document.

Compound **11** of Link also includes an amide substituent at the carbon alpha to the carbonyl. Applicant claims a group of compounds with a precisely limited group of possible substituents alpha to the heterocycle-carbonyl group. Substitution with Link's amide group actually destroys FAAH inhibitory activity. Thus, one skilled in the art would not combine the teachings of Link with those of the Boger PNAS document because Link teaches protease inhibitors, and even if the teachings of Link and the Boger PNAS document were combined, one would not arrive at a FAAH inhibitor as claimed by Applicant because the Link compounds each appear to require amides or sulfoxide moieties.

The Office Action asserts that one would be motivated to modify the compounds of Link by deleting groups taught by Boger et al. However, a suggestion to employ such deletions would require impermissible hindsight, not the application of ordinary skill in the art. The Office Action does not explained why one of skill in the art would delete the amide-containing substituent instead of the phenylethyl substituent or the phenyl substituent of the oxazole, none of which are found in the disclosure of the Boger PNAS document. Such deletions (in favor of additional substitutions) are not merely choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success. Only by using hindsight could one combine the disclosures of Link and the Boger PNAS document and arrive at Applicant's claimed compounds. Thus a *prima facie* case of obviousness cannot be maintained against the claims for the combination of Link and the Boger PNAS document. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Applicant further points out that even the deletion of the 3-cyclohexylpropionamide moiety of Link's compound **11** does not result in a compound that falls within the scope of Applicant's new claims 9-15. Further hindsight and modification would be necessary to arrive at the subject matter of claims 9-15 and neither Link nor the Boger PNAS document provide any teaching or suggestion to substitute the oxazole moiety as claimed by applicant. Accordingly, Claims 9-15 are believed to be in condition for allowance, and notification to that effect is earnestly requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's representative at (612) 359-3270 to facilitate prosecution of this application.

If necessary, please charge any additional fees or deficiencies, or credit any overpayments to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on April 22, 2009.

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